Letter to the Editor

D-dimer: A biomarker for antihistamine-resistant chronic urticaria

To the Editor:

Chronic urticaria (CU) may affect up to 1% of the general population at some point in life and can severely impair quality of life. Most patients respond satisfactorily to antihistamines, but some are unresponsive and only part of these show a particularly severe disease. We recently found that CU is characterized by an activation of coagulation cascade paralleling disease severity.[1] The activation pathway involved is related to tissue factor[2] expressed by the eosinophils present in the inflammatory infiltrate,[3] and in some patients, the activation may be intense enough to lead to an elevation in plasma levels of D-dimer, a marker of fibrinolysis.[4] Thrombin is able to activate mast cells, triggering their degranulation. D-dimer measurement is easily available and thus represents a potentially ideal candidate prognostic marker for CU; its usefulness as a predictor of response to antihistamines was studied here.

Ninety-one patients (male/female 22/69; mean age, 46.9 years; range, 11-85; median, 47) with spontaneous CU were studied. The mean disease duration was 28.6 months (median, 5; range, 2-240). To assess autoreactivity and disease severity, all antihistamine therapies were stopped on the first visit, and patients filled-up a standardized questionnaire about the severity of pruritus and wheals on days 5 to 7 off antihistamines to calculate the mean urticaria activity score (UAS).[5] All patients were then given cetirizine 10 mg/d for 7 to 14 days as a standard treatment; in case of little or no response, the dosage was increased 2-fold for 4 days and then 3-fold for 3 further days. Patients assessed the response to cetirizine by quantifying their wheals and pruritus before and after the treatment on a visual analog scale.

Response to antihistamine treatment was graded as follows:

- Excellent: complete disappearance of pruritus and wheals under cetirizine at licensed dose
- Good: nearly complete (ie, >75%) disappearance of pruritus and wheals with cetirizine at licensed dose or at higher doses
- Partial: 50% to 75% clinical improvement by cetirizine at higher than licensed doses
- Poor: 25% to 50% clinical improvement by cetirizine even at higher than licensed dose.
- Absent: no response at any dose of cetirizine.

Fifty-one of 91 patients underwent an autologous plasma skin test (APST; n = 37) and/or an autologous serum skin test (ASST; n = 16) to assess auroreactivity on days 5 to 7 off antihistamines.

Patients performed *in vitro* analyses at hospital sites closest to their homes or workplaces. Plasma D-dimer levels were measured by using ELISA 7 to 14 days after the first visit, while patients were taking antihistamines and before any immunosuppressive treatment was started in nonresponders, and were expressed in ng/mL. Because of the existence of various cutoffs as a consequence of differences in standardization between the various producers of the assay kits, plasma levels were classified as "normal" (within the normal range for that particular method) or "elevated." Thyroid autoantibodies, C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR) were measured in all patients as well.

All clinical investigations were carried out according to the principles of the Declaration of Helsinki; all patients gave their informed consent to diagnostic procedures. Because the study was based on data stemming from routine clinical activity, approval by an ethics committee was not needed. Proportions were compared by using the χ^2 test with Yates' correction. Probability values of less than 5% were considered statistically significant.

The mean average UAS in the study population was 3.6 (median, 4; range, 2-5). The response to cetirizine was "excellent" in 41 (45%) patients, "good" in 14 (15%), "partial" in 5 (5%), "poor" in 23 (25%), and "absent" in 8 (9%). Autoreactivity was detected in 31 of 37 (86%) patients by APST and in 8 of 16 (50%) patients by ASST. Both patients who underwent both tests scored positive on the APST and negative on the ASST. D-dimer plasma levels were elevated in 30 of 91 (33%) patients. Eighteen (20%) patients showed circulating thyroid autoantibodies, and ESR and CRP were elevated in 5 (6%) and 7 (8%) patients, respectively. Plasma D-dimer levels were elevated in 0 of 41 (0%) patients showing an "excellent" response to cetirizine, 3 of 14 (21%) patients showing a "good" response, 3 of 5 (60%) patients showing a "partial" response, 18 of 23 (78%) patients showing a

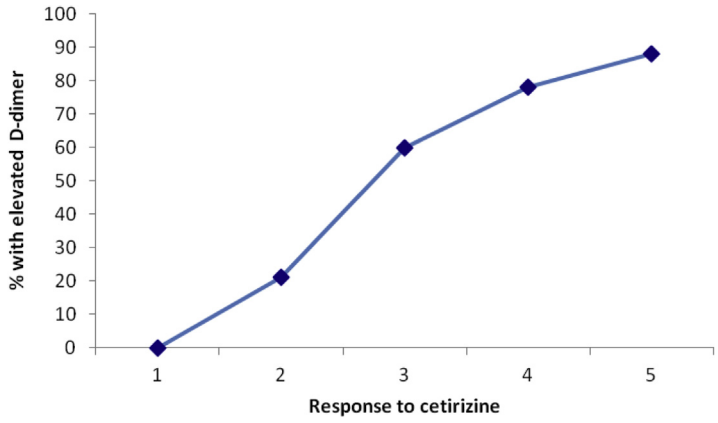

FIG 1. Proportion of patients with CU showing elevated D-dimer plasma levels as a function of clinical response to cetirizine. x-axis: 1, excellent; 2, good; 3, partial; 4, poor; 5, no response to the drug.

TABLE I. Clinical response to cetirizine in patients with different CU severity in function of D-dimer levels

UAS	D-dimer	Excellent or good response to cetirizine	*P* value
2	Normal	6/6 (100%)	—
2	Elevated	0/0	
3	Normal	27/29 (93%)	<.001
3	Elevated	1/7 (14%)	
4	Normal	20/23 (87%)	<.001
4	Elevated	2/13 (15%)	
5	Normal	0/3 (0%)	NS
5	Elevated	0/10 (0%)	

NS, Not significant.

"poor" response, and 7 of 8 (88%) nonresponders (Fig 1). On comparing patients with a disease of similar severity showing either normal or elevated D-dimer levels, it turned out that the latter were much more frequently cetirizine-resistant, particularly when urticaria severity was moderate ($P < .001$ for both patients with UAS 3 and 4; Table I). Fig 2 shows the individual D-dimer levels in patients with CU of different severity. After "normalization" to a cutoff level of 500 ng/mL, in those showing elevated D-dimer levels, the mean plasma levels were 697 (range, 696-1163) in 3 subjects showing a "good" response to cetirizine, 634 (542-1306) in 3 subjects showing a "partial" response, 875 (542-2490) in 17 patients showing a "poor" response, and 981 (723-2450) in 7 nonresponders. Elevated D-dimer levels did not correlate with thyroid autoimmunity (coincidence in only 6 of 18 [33%] patients with thyroid autoimmunity), but did with elevated CPR (6 of 8 [75%]) and elevated ESR (3 of 5 [60%]) levels. Follow-up data were available for 3 patients; in 2 patients unresponsive to cetirizine at any dosage and showing elevated D-dimer levels, plasma levels dropped to the normal range following treatment with heparin and tranexamic acid[6] in coincidence with periods of effectiveness of antihistamine treatment alone; in the other case, D-dimer levels dropped from 450 to 410 ng/mL and then to 300 ng/mL (normal value < 280) within 3 months under ciclosporin therapy; the last measurement was in coincidence with a much better control of the disease.

This study group was highly representative of the CU population: females prevailed, autoreactivity was present in 50% by the ASST and in 86% by the APST,[1] 20% showed thyroid autoimmunity, the median disease duration was 5 months, and disease severity was well distributed between 2 and 5 UAS. Patients with severe CU often show elevated plasma levels of D-dimer,[4] and some of them may benefit dramatically from anticoagulant therapy,[6] suggesting that coagulation factors might play a pathogenic role that goes well beyond that of innocent bystanders. Heparin, oral anticoagulants, and other drugs interfering with the coagulation such as synthetic protease inhibitors have been also effective in some patients with unremitting CU. This study suggests that elevated D-dimer levels can be considered as a biomarker for antihistamine-resistant CU, particularly in patients showing a moderate disease severity. If coagulation factors acted uniquely, activating mast cells, a good response to antihistamines should be expected anyway. However, often this is not the case, suggesting that mediators other than histamine may be sometimes involved, making antihistamines ineffective at any dosage. In effect, in animal models, thrombin not only activates protease-activated receptor-1 on mast cells but also increases vascular permeability acting directly on endothelial cells and bypasses the first part of the complement cascade by generating C5a in the absence of C3.[7] However, D-dimer levels may also be elevated in angioedema because of C1-inhibitor deficiency[8] and in nonallergic asthma,[9] 2 diseases in which antihistamines show little or no efficacy. The possibility that in patients with CU showing an activation of fibrinolysis a supplementary mechanism of inflammation is operative is suggested by the different response to cetirizine observed in subjects with CU of the same severity with or without elevated D-dimer levels. In this respect, CU is also characterized by elevated vascular endothelial growth factor, one of the major mediators of vascular permeability, expressed by skin eosinophils, which parallels disease severity and is associated with plasma levels of fragment F1+2 and, hence, with the

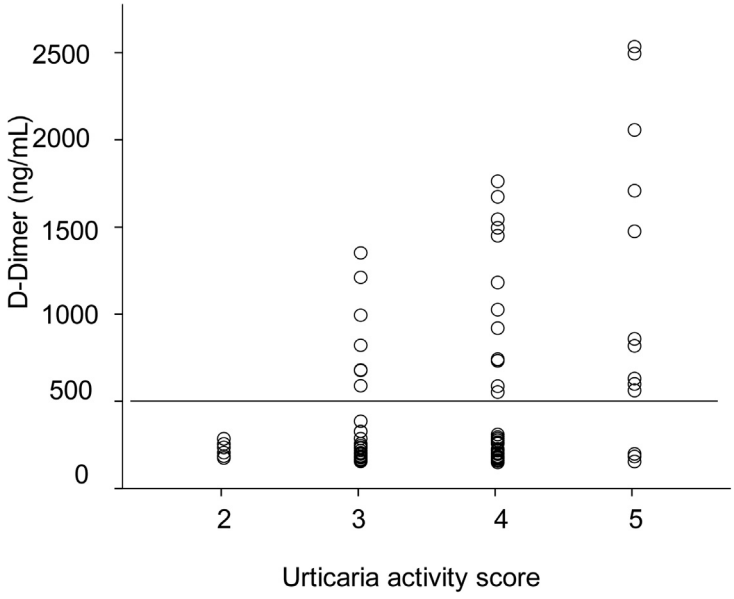

FIG 2. Individual levels of D-dimer in patients showing CU of different severity.

activation of the coagulation cascade.[10] Of course, it is also possible that D-dimer simply increases as other acute phase parameters do, without any participation of the coagulation cascade in the pathogenic mechanisms underlying antihistamine-resistant urticaria.

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